FIG. 1

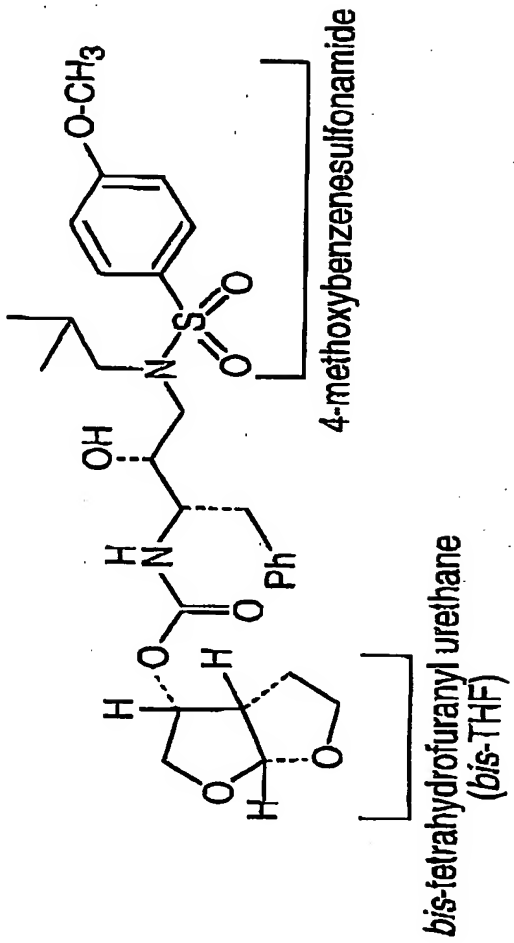

O-CH3
S
O
O
N
OH
H
N
Ph
O
O
H
H
O
O
H
4-methoxybenzenesulfonamide
bis-tetrahydrofuranyl urethane
(bis-THF)

FIG. 2

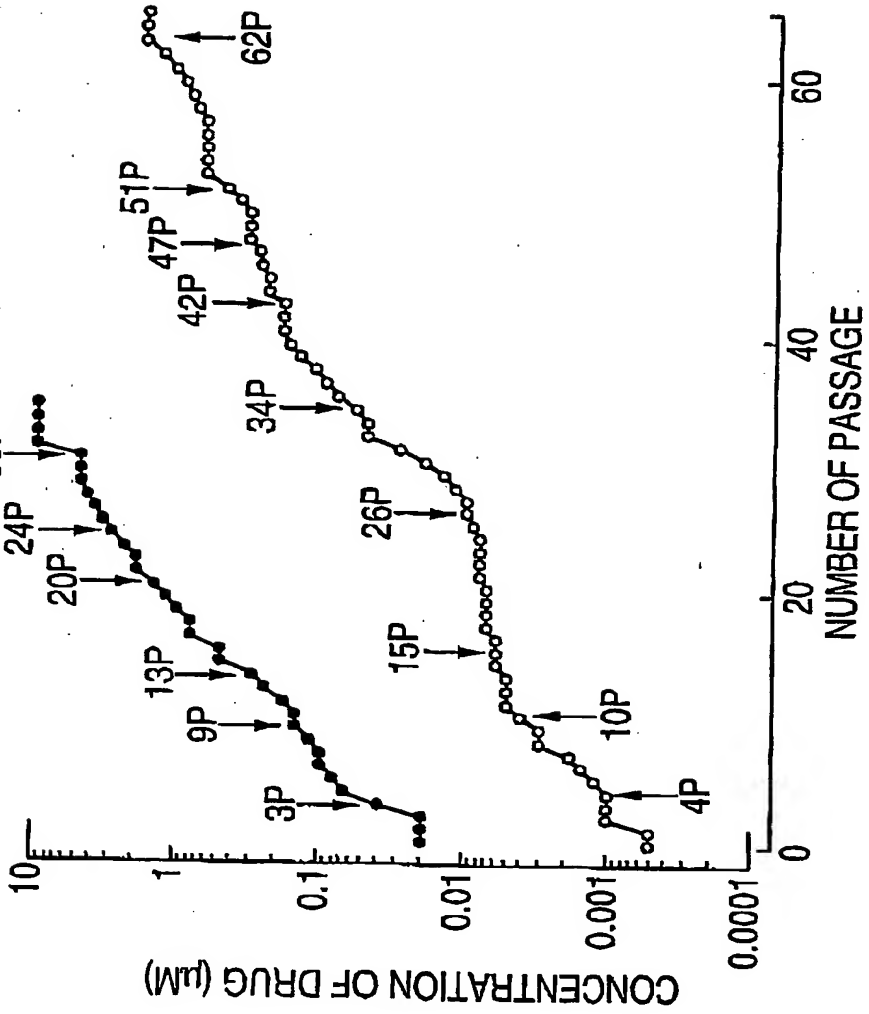

62P
51P
47P
42P
34P
30P
26P
24P
20P
15P
13P
10P
9P
4P
3P
10
1
0.1
0.01
0.001
0.0001
CONCENTRATION OF DRUG (μM)
0
20
40
60
NUMBER OF PASSAGE

FIG. 3A

	10 20 30 40 50 60 70 80 90 99	FRACTION OF CLONES
pNL-4-3	:PQITLWQRPL VTIKIGGQLK EALLDTGADD TVLEEMNLPG RWKPKMIGGI GGFIKVRQYD QILIEICGHK AIGTVLVGPT PVNIIGRNLL TQIGCTLNF	
P4-1	:.....:.....:.....:.....:.....:.....:.....:.....:.....:.....:	8/8
P10-1	:.....:.....:.....:.....:.....:.....:.....:.....:.....:.....:	6/16
P10-2	:.....:.....:.....:.....:.....:.....V.....:.....:.....:.....:	2/16
P10-3	:.....:.....:.....:.....:.....:.....T.....:.....:.....:.....:	2/16
P10-4	:.....K.....:.....:.....:.....:.....:.....:.....:.....:.....:	1/16
P10-5	:.....M.....:.....:.....:.....:.....:.....:.....:.....:.....:	1/16
P10-6	:.....:.....:.....R.....:.....:.....:.....:.....:.....:.....:	1/16
P10-7	:.....:.....:.....:.....:.....:.....S.....:.....:.....:.....:	1/16
P10-9	:.....:.....:.....:.....:.....:.....:.....I.....:.....:.....:	1/16
P10-10	:.....:.....:.....:.....:.....:.....:.....V.....:.....:.....:	1/16
P15-1	:.....:.....:.....:.....R.....:.....:.....:.....I.....:.....:	2/9
P15-2	:.....:.....:.....S.....:.....:.....:.....:.....I.....:.....:	2/9
P15-3	:.....:.....:.....A.S.....:.....:.....:.....:.....:.....:.....:	1/9
P15-4	:.....:.....:.....S.....R.....:.....T.....:.....:.....:.....:	1/9
P15-5	:.....:.....:.....S.....:.....:.....:.....:.....:.....:.....:	1/9
P15-6	:.....:.....:.....:.....:.....:.....:.....:.....I.....:.....:	1/9
P15-7	:.....:.....:.....:.....:.....:.....:.....:.....I.....:.....:	1/9
P26-1	:.....:.....:.....:.....:.....:.....:.....:.....I.....:.....:	3/10
P26-2	:.....:.....:.....S.....:.....:.....:.....:.....:.....:.....:	2/10
P26-3	:.....F.....:.....S.....:.....:.....:.....:.....I.....:.....:	1/10
P26-4	:.....:.....:.....S.....:.....:.....:.....T.....I.....:.....:	1/10
P26-5	:.....:.....:.....S.....:.....:.....:.....V.....:.....:.....:	1/10
P26-6	:.....:.....:.....I.....:.....I..V.....:.....V.....:.....:.....:	1/10
P26-7	:.....R.....:.....:.....:.....I..V.....:.....V.....:.....:.....:	1/10

FIG. 3B

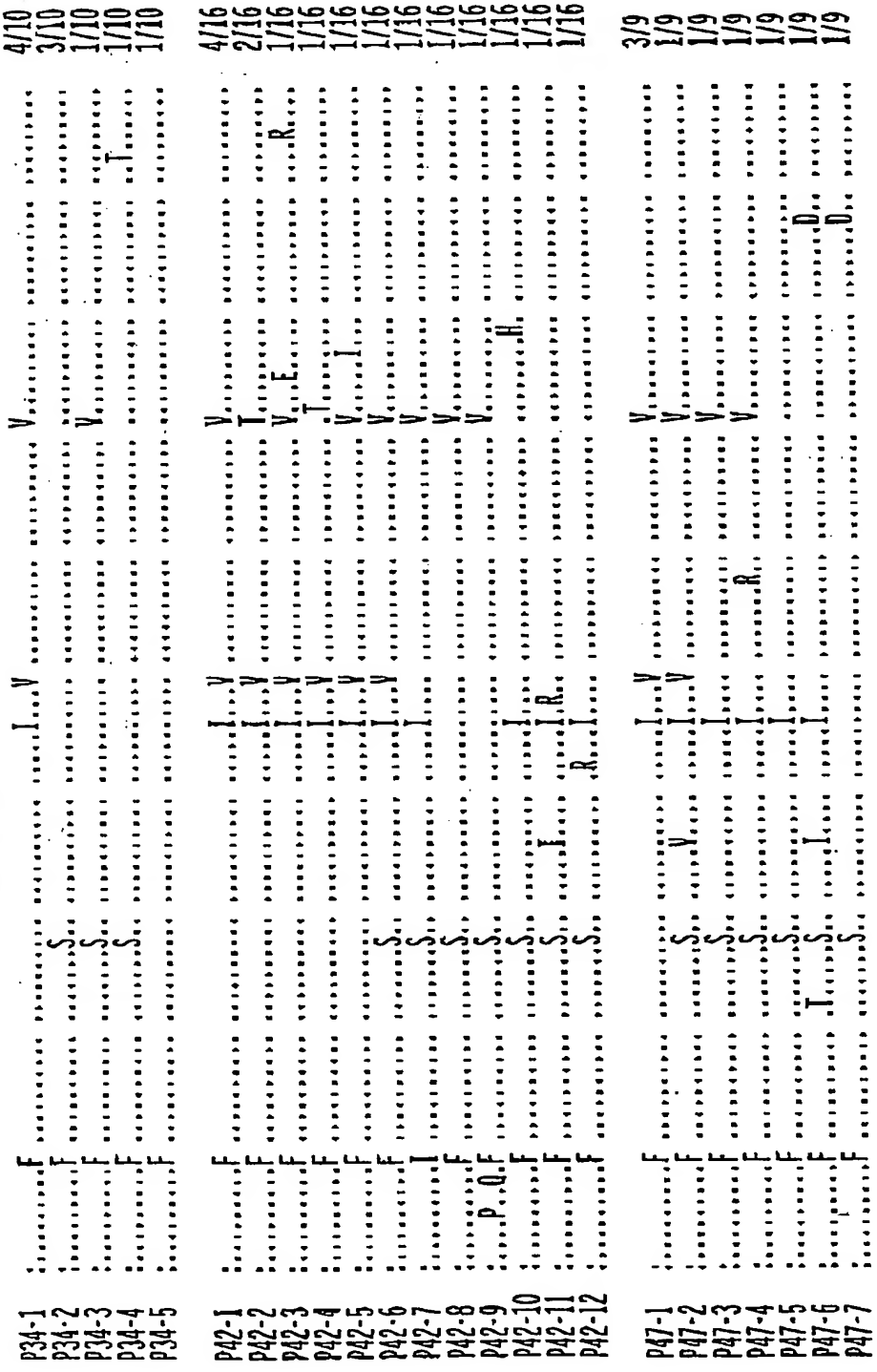

P34-1 4/10
P34-2 3/10
P34-3 1/10
P34-4 1/10
P34-5 1/10
P42-1 4/16
P42-2 2/16
P42-3 1/16
P42-4 1/16
P42-5 1/16
P42-6 1/16
P42-7 1/16
P42-8 1/16
P42-9 1/16
P42-10 1/16
P42-11 1/16
P42-12 1/16
P47-1 3/9
P47-2 1/9
P47-3 1/9
P47-4 1/9
P47-5 1/9
P47-6 1/9
P47-7 1/9

FIG. 3C

P51-1	.....F .....S.. .....I...V ..... V.....	3/9
P51-2	.....F .....S.. .....I...V ..... V.S.....	1/9
P51-5	.....F .....S.. .....I..... ..... V.....	1/9
P51-6	.....F .....S.. .....I..... ..... V.....	1/9
P51-7	.....F .....S.. .....I..... ..... V..... ....S	1/9
P51-8	.....F .....S.. .....I..... ..... L..... ..... .D..	1/9
P51-9	.....F .....S.. .....I..... .... .D.. .L.....	1/9
P62-1	.....F .....S.. .....I..... .... .D..	2/11
P62-2	.....F .....S.. .....I..... ..... V..... ..... .D..	1/11
P62-3	.....F .....S.. .....I..E ..... V.....	1/11
P62-4	.....F .....S.. .....I..... ..... V.....	1/11
P62-5	.....F .....S.. .....I.....	1/11
P62-6	.....F ....I..... ..... V..... ..... .D..	1/11
P62-7	.....F ....I...V ....Y... V..... ..... .D..	1/11
P62-8	.....P.....F ....I...V ..... V.....	1/11
P62-9	.....P.....F ....I...V	1/11
P62-10	.....F ....I...V ..... V.....	1/11

SEQUENCE ANALYSIS OF THE PROTEASE-ENCODING REGION OF HIV-1 PASSAGED IN THE PRESENCE OF UIC-94003. THE AMINO ACID SEQUENCES OF PROTEASE DEDUCED FROM NUCLEOTIDE SEQUENCES OF THE PROTEASE-ENCODING REGION OF HIV-1 CLONES DETERMINED AT NINE DIFFERENT PASSAGES ARE ILLUSTRATED. THE FRACTION OF CLONES EXAMINED IS INDICATED ON THE RIGHT. THE AMINO ACID SEQUENCE OF PROTEASE OF A WILD-TYPE pNL4-3 CLONE IS SHOWN AS A REFERENCE. IDENTITY WITH THIS SEQUENCE AT INDIVIDUAL AMINO ACID POSITIONS IS INDICATED (DOTS).

FIG. 4

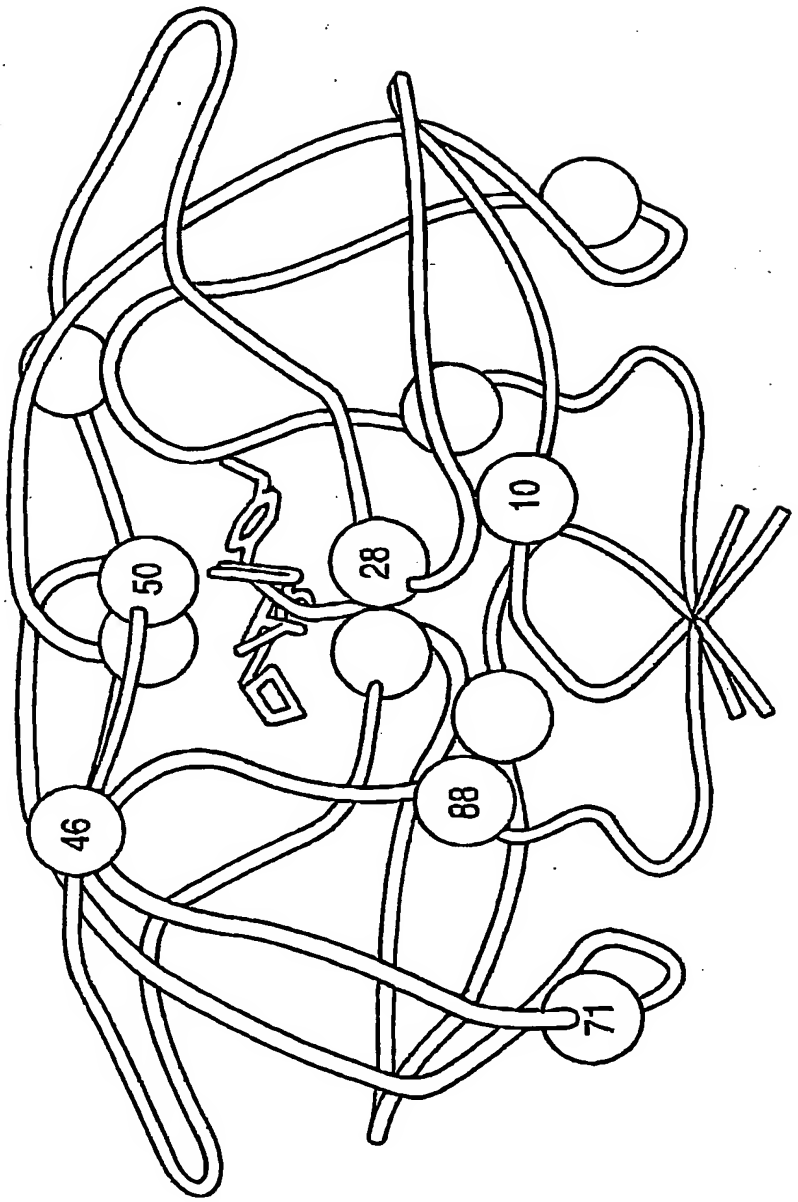


FIG. 5

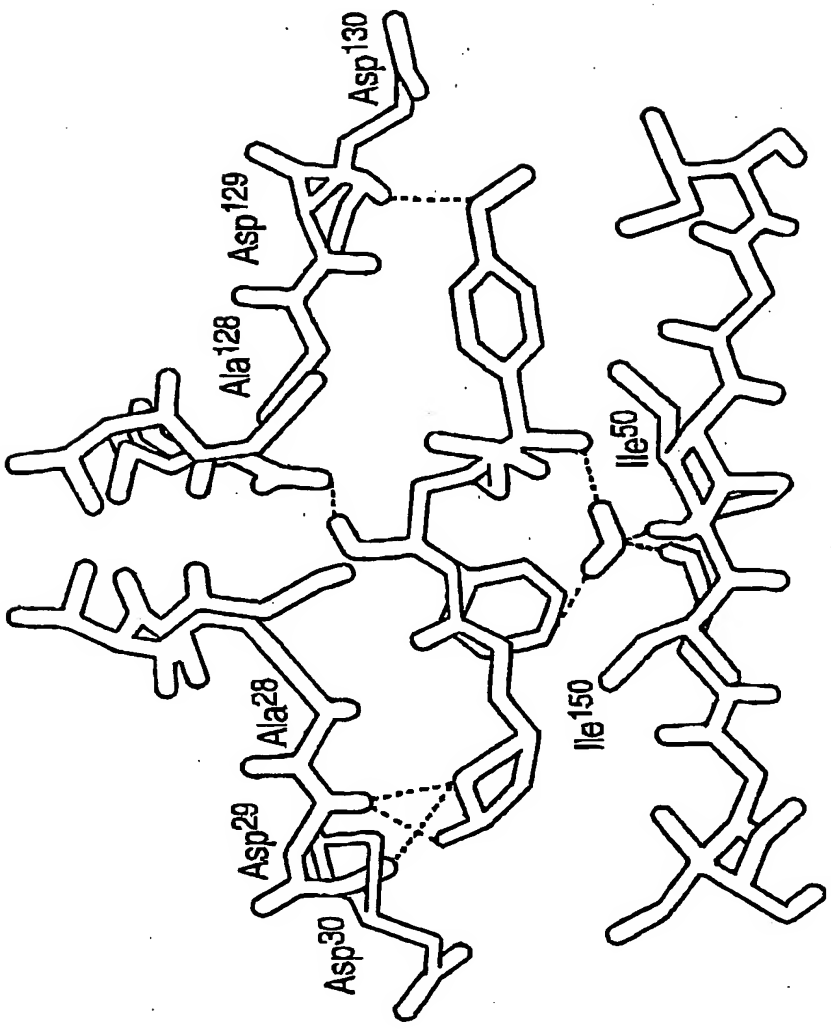
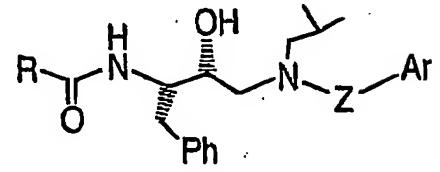
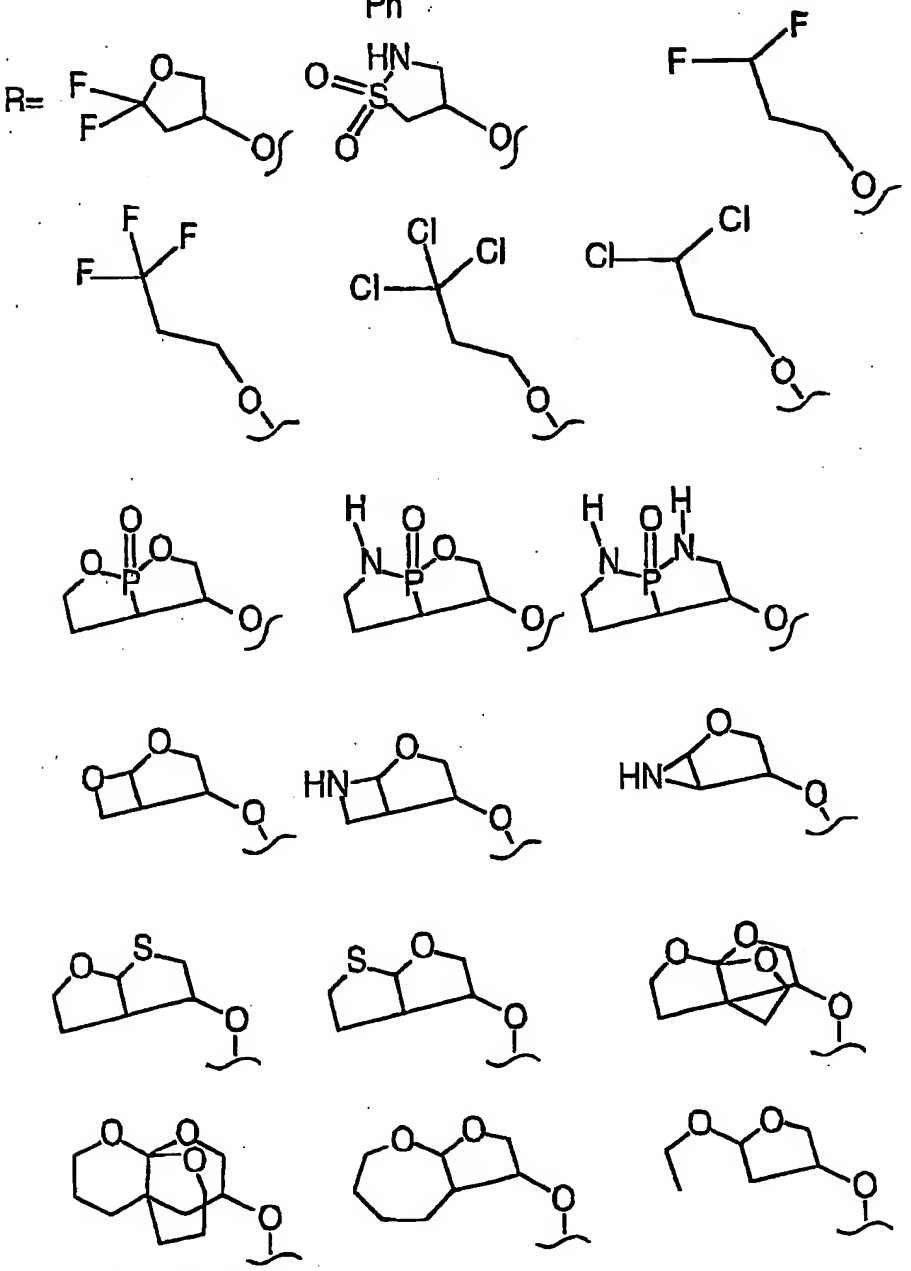


FIG. 6

WHERE:



R=



WHERE Z IS, FOR EXAMPLE, -S(O)$_2$-, -C(O)-, -C(O)-NH-, OR -C(O)-O-, AND WHERE Ar IS, FOR EXAMPLE, 4-METHOXYPHENYL, 4-AMINOPHENYL, PHENYL, 4-METHYLAMINOPHENYL, OR 4-PYRIDYL

FIG. 7A

Table 8

Atom	x [Å]	y [Å]	z [Å]	σ [Å]	Description
Substructure of the protein					
O301	-7.9	13.6	27.4	0.5	Oxygen atom of water molecule coordinated to main chain amide nitrogen atoms of amino acid Gly 49 and Gly149
O27	-13.8	17.7	30.4	0.5	Main Chain carbonyl oxygen atom of amino acid Gly 27
N29	-13.4	18.2	34.5	0.5	Main chain amide nitrogen atom of amino acid Asp 29
N30	-11.9	18.6	36.7	0.5	Main chain amide nitrogen atom of amino acid Asp 30
OD1 25	-11.3	21.2	28.7	0.5	Carboxylate oxygen atom of aminoacid Asp 25
OD2 25	-9.4	20.4	29.3	0.5	Carboxylate oxygen atom of aminoacid Asp 25
OD1 125	-12.7	20.3	26.4	0.5	Carboxylate oxygen atom of aminoacid Asp 125
OD2 125	-12.7	20.3	26.4	0.5	Carboxylate oxygen atom of aminoacid Asp 125
N129	-8.9	20.5	20.7	0.5	Main chain amide nitrogen atom of amino acid Asp 129
N130	-10.1	19.5	18.6	0.5	Main chain amide nitrogen atom of amino acid Asp 130
Substructure of the inhibitor					
HD:A	-8.8	17.5	25.7	0.5	Interacting with main chain carbonyl oxygen

FIG. 7B

					atom of amino acid Gly 27
HA:A	-8.5	15.3	25.1	0.5	Interacting with Oxygen atom of water molecule coordinated to main chain amide nitrogen atoms of amino acid Gly 49 and Gly149
HD/A:B	-10.4	19.1	27.4	0.5	Interacting with carboxylate oxygen atoms of aminoacids Asp 25 and Asp 125
HA:A'	-8.9	14.0	29.8	0.5	Interacting with Oxygen atom of water molecule coordinated to main chain amide nitrogen atoms of amino acid Gly 49 and Gly149
HA1:X	-8.6	17.3	20.7	0.5	Main chain amide nitrogen atom of amino acid Asp 30
HA2:X	-6.9	18.7	21.4	0.5	Interacting with main chain amide nitrogen atom of amino acid Asp 29
HA:X'	-10.7	15.8	35.8	0.5	Interacting with main chain amide nitrogen atom of amino acid Asp 130

TABLE 1

SENSITIVITIES OF HIV-1_{LAI}, HIV-1_{Ba-L}, AND HIV-2_{EHO} TO VARIOUS RTIs AND PIs[a]

		MEAN IC_{50} (μM) ± SDs									
		RTIs				PIs					
VIRUS	CELLS	AZT	ddI	3TC	RTV	IDV	SQV	NFV	APV	UIC-94003
HIV-1_{LAI}	PBMC	0.003 ± 0.0002	0.62 ± 0.02	0.021 ± 0.018	0.04 ± 0.008	0.015 ± 0.004	0.011 ± 0.005	0.009 ± 0.0003	0.017 ± 0.003	0.0003 ± 0.000009
HIV-1_{Ba-L}	PBMC	0.011 ± 0.007	1.5 ± 1.1	0.054 ± 0.046	0.038 ± 0.02	0.017 ± 0.011	0.014 ± 0.01	0.003 ± 0.002	0.023 ± 0.009	0.0003 ± 0.000004
HIV-1_{LAI}	MT-2	0.024 ± 0.003	3.4 ± 0.2	0.65 ± 0.01	0.041 ± 0.005	0.019 ± 0.009	0.023 ± 0.002	0.005 ± 0.002	0.041 ± 0.01 -	0.0003 ± 0.0001
HIV-2_{EHO}	MT-2	0.003 ± 0.001	2.8 ± 0.6	0.4 ± 0.25	0.35 ± 0.025	0.01 ± 0.004	0.004 ± 0.0005	0.02 ± 0.01	0.53 ± 0.03	0.0005 ± 0.000007

[a] DATA SHOWN REPRESENT MEAN VALUES (WITH STANDARD DEVIATIONS) DERIVED FROM THE RESULTS OF THREE INDEPENDENT EXPERIMENTS CONDUCTED IN DUPLICATE OR TRIPLICATE. FOR PBMC, THE (IC_{50} WERE DETERMINED BY EMPLOYING PHA-PBMC EXPOSED TO EACH HIV-1 PREPARATION (50 $TCID_{50}$s PER 10^6 PBMC) IN THE PRESENCE OF EACH ANTI-HIV-1 AGENT AND USING THE INHIBITION OF $p24^{Gag}$ PROTEIN PRODUCTION AS AN ENDPOINT ON DAY 7 OF CULTURE. MT-2 CELLS (2×10^3) WERE EXPOSED TO 100 $TCID_{50}$s OF HIV-1_{LAI} OR HIV-2_{EHO} AND CULTURED IN THE PRESENCE OF VARIOUS CONCENTRATIONS OF RTIs OR PIs, AND THE IC_{50}s WERE DETERMINED USING THE MTT ASSAY ON DAY 7 OF CULTURE. ABBREVIATIONS: AZT, ZIDOVUDINE; ddI, DIDANOSINE; 3TC, LAMIVUDINE; RTV, RITONAVIR; IDV, INDINAVIR; SQV, SAQUINAVIR; NFV, NELFINAVIR; APV, AMPRENAVIR.

TABLE 2

SENSITIVITIES OF HIV-1 ISOLATED FROM; HEAVILY DRUG-EXPERIENCED INDIVIDUALS TO PIs

VIRUS	AMINO ACID SUBSTITUTIONS IN PR-ENCODING REGION[a]	IC_{50}[b] μM (FOLD CHANGE)					
		RTV	IDV	SQV	NFV	APV	UIC-94003
WILD TYPE	L63P	0.044(1)	0.013(1)	0.019(1)	0.023(1)	0.025(1)	0.0007(1)
1	L10I, K14R, L33I, N37I, M46I, F53L, K55R, I62V, L63P, A71V, G73S, V82A, L90M, I93L	>1(>23)	>1(>77)	0.27(27)	>1(>43)	0.27(11)	0.004(6)
2	L10I, I15V, K20R, M36I, M46L, I54V, K55R, I62V, L63P, K70Q, V82A, L89K	>1(>23)	0.49(38)	0.037(4)	0.33(14)	0.28(11)	0.0013(2)
3	L10I, I15V, E35D, N37E, K45R, I54V, L63P, A71V, V82T, L90M, I93L, C95F	>1(>23)	0.49(38)	0.035(4)	>1(>43)	0.26(10)	0.001(1)
4	L10I, V11I, T12E, I15V, L19I, R41K, M46L, L63P, A71T, V82A, L90M	>1(>23)	0.21(16)	0.033(3)	0.09(4)	0.31(12)	0.0016(2)
5	L10I, K43T, M46L, I54L, L63P, A71T, V82A, L90M, Q92K	>1(>23)	>1(>77)	0.31(31)	0.41(18)	0.67(27)	0.0024(3)
6	L10I, K14R, R41K, M46L, I54V, L63P, A71V, V82A, L90M, I93L	>1(>23)	0.30(23)	0.19(19)	>1(>43)	0.16(6)	0.0035(1)
7	L10I, L24I, L33F, E35D, M36I, N37S, M46L, I54V, R57K, I62V, L63P, A71V, G73S, V82A	>1(>23)	>1(>77)	0.12(12)	>1(>43)	0.49(20)	0.0055(8)
8	L10R, M37D, M46I, I62V, L63P, A71V, G73S, V77I, V82T, L90M, I93L	>1(>23)	0.55(42)	0.042(4)	>1(>43)	0.15(6)	0.001(1)

[a] THE AMINO ACID SEQUENCE OF EACH VIRAL ISOLATE WAS DEDUCED FROM THE NUCLEOTIDE SEQUENCE AND COMPARED TO THE CONSENSUS B SEQUENCE CITED FROM THE LOS ALAMOS DATA BASE. A CLINICAL ISOLATE, HIV-$1_{ERS104pre}$ (31), SERVED AS A SOURCE OF WILD-TYPE HIV-1.

[b] THE IC_{50} WERE DETERMINED BY EMPLOYING PHA-PBMC EXPOSED TO HIV-1 STRAINS (50 $TCID_{50}$S PER 10^5 PBMC) IN THE PRESENCE OF EACH ANTI-HIV-1 AGENT AND USING THE INHIBITION OF $p24^{Gag}$ PROTEIN# PRODUCTION AS AN ENDPOINT. ALL VALUES HERE DETERMINED IN TRIPLICATE, AND THOSE SHOWN ARE REPRESENTATIVE OF TWO OR THREE SEPERATE EXPERIMENTS. NUMBERS IN PARENTHESES REPRESENT FOLD CHANGES OF IC_{50}S AGAINST EACH ISOLATE COMPARED TO IC_{50}S AGAINST HIV-1_{WT}.

SEE TABLE 1, FOOTNOTE *a*, FOR ABBREVIATIONS.

TABLE 3

AMINO ACID SUBSTITUTIONS IN PR AND SENSITIVITIES OF DRUG-RESISTANT HIV-1 STRAINS TO PIs[a]

VIRUS	AMINO ACID SUBSTITUTIONS	IC_{50}, μM (FOLD CHANGE)					
		RTV	IDV	APV	SQV	NFV	UIC-94003
$HIV\text{-}1_{HL4\text{-}3}$		0.038(1)	0.011(1)	0.042(1)	0.019(1)	0.023(1)	0.0003(1)
$HIV\text{-}1_{UIC\text{-}P62}$	L10F, A28S, M46I, I50V, A71V, N88D	0.055(1)	0.08 (7)	0.83(20)	0.01(1)	0.11(5)	0.021(70)
$HIV\text{-}1_{APV\text{-}P30}$	L10F, V32I, M46I, I54M, A71V, I84V	>1.0(>26)	0.32(30)	>1.0(>25)	0.035(2)	>1.0(43)	0.029(100)

[a] MT-2 CELLS (2 X 10^3) WERE EXPOSED TO $HIV\text{-}1_{HL4\text{-}3}$, $HIV\text{-}1_{UIC\text{-}P62}$, OR $HIV\text{-}1_{APV\text{-}P30}$(ALL 100 $TCID_{50}$s) AND CULTURED IN THE PRESENCE OF VARIOUS DRUG CONCENTRATIONS. THE IC_{50}s WERE DETERMINED ON DAY 7 OF CULTURE IN THE MTT ASSAY. ALL VALUES WERE DETERMINED IN DUPLICATE, AND THOSE SHOWN ARE REPRESENTIVE OF TWO OR THREE INDEPENDENT EXPERIMENTS. THE NUMBERS IN PARENTHESES REPRESENT FOLD CHANGES COMPARED TO $HIV\text{-}1_{HL4\text{-}3}$ (WILD TYPE). SEE TABLE 1, FOOTNOTE *a*, FOR ABBREVIATIONS.